

ORIGINAL ARTICLE

Pharmacokinetics of oral mycophenolate mofetil in combination with CsA in dogs after nonmyeloablative allogeneic hematopoietic stem cell transplantation

S Lange¹, SC Mueller², S Altmann¹, M Dahlhaus¹, B Drewelow², M Freund¹ and C Junghanss¹

¹Department of Hematology/Oncology, Division of Medicine, University of Rostock, Rostock, Germany and ²Department of Clinical Pharmacology, Institute of Experimental/Clinical Pharmacology and Toxicology, University of Rostock, Rostock, Germany

Mycophenolate mofetil (MMF) has been used successfully in solid organ transplantation (SOT) and more recently in nonmyeloablative hematopoietic stem cell transplantation (HSCT) for prophylaxis of graft rejection and acute graft-versus-host disease. However, the pharmacokinetics of MMF seem to differ when applied in HSCT compared to SOT. Here, we analyzed pharmacokinetics of mycophenolic acid (MPA), the active metabolite of MMF, in a nonmyeloablative canine HSCT model. Dogs received nonmyeloablative TBI for conditioning followed by leukocyte antigen-identical littermate HSCT and immunosuppression containing cyclosporin A (CsA) and different doses of MMF. Pharmacokinetics were performed on days 2, 14 and 27. Dose escalation of MMF from 10 to 30 mg/kg tended to increase area under the curve (AUC) and the apparent oral clearance by 45 and 110%, respectively. Doses applied had no linear association with MPA concentration or blood trough level. No significant drug accumulation occurred over time. Using a twice daily MMF regimen, we conclude that an AUC of 30–60 µg/ml h as recommended for SOT cannot be reached in HSCT. Toxicities did not permit single doses higher than 30 mg/kg. Thus, if larger AUCs are desired in order to assure sufficient immunosuppression in HSCT, MMF might have to be administered at least three times daily.

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Introduction

Mycophenolate mofetil (MMF; CellCept; Roche, Grenzach-Wyhlen, Germany) is an effective immunosuppressant that has been used successfully in solid organ transplantation (SOT) for prophylaxis of graft rejection since the 1990s.^{1,2} MMF is an ester prodrug of mycophenolic acid (MPA) which inhibits inosine monophosphate dehydrogenase and thus blocks the *de novo* pathway of guanosine synthesis in T and B lymphocytes. Following oral administration MMF is rapidly and completely absorbed and hydrolyzed to the active immunosuppressive drug MPA. MPA is further metabolized by glucuronosyl-transferase enzymes in the intestine, liver and kidneys to form a glucuronide conjugate (mycophenolic acid glucuronide (MPAG)). In the gastrointestinal tract the pharmacologically inactive MPAG is deglucuronidized by β-glucuronidases of the normal gut flora. Hence, MPA is restored and enterohepatically recycled, which is represented by a characteristic secondary MPA peak that occurs 6–12 h after dosing and may account for up to 40% of the area under the curve (AUC).³

Apart from SOT, MMF is increasingly used in nonmyeloablative hematopoietic stem cell transplantation (HSCT). In preclinical studies a nonmyeloablative HSCT regimen was established in dogs that employed a pre-transplant conditioning with 2 Gy TBI along with a post transplant immunosuppression consisting of cyclosporin A (CsA) and MMF.⁴ Based on these canine studies the combination of CsA and MMF is now commonly used after nonmyeloablative conditioning regimens for prevention of graft rejection and graft-versus-host disease. So far, limited data regarding the pharmacokinetic profile of MMF after HSCT are available. First investigations in humans showed a shortening of half-life of the active metabolite MPA in HSCT patients relative to SOT patients or healthy volunteers.⁵ In addition, perturbations of enterohepatic recycling following HSCT were observed.⁶ This resulted in MPA concentrations below the therapeutic range recommended for SOT.⁷ Furthermore, correlations of MPA plasma concentrations at steady state and AUC with degree of T-cell chimerism⁸ and incidence of graft rejection^{6,8} have been suggested.

Correspondence: Dr C Junghanss, Department of Hematology/Oncology, Division of Medicine, University of Rostock, Ernst-Heydemann-Street 6, Rostock 18057, Germany.

E-mail: christian.junghanss@med.uni-rostock.de

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In order to better characterize the pharmacokinetics of MPA in the HSCT setting we evaluated plasma concentrations of MPA in the well-established canine HSCT model. This model has been proven to be a very suitable model to answer questions regarding HSCT but also pharmacokinetics. The dog has closer genetic proximity with humans than rodents.⁹ Its body size and similarities within metabolic pathways between dogs and humans also provide a good basis for pharmacokinetic studies.¹⁰

Materials and methods

All experiments were approved by the review board of the state Mecklenburg-Vorpommern (State Institute for Agriculture, Food Safety and Fishery Mecklenburg-Vorpommern, Germany).

Laboratory animals and DLA typing

Litters of random-bred beagles were purchased from commercial kennels possessing a license for animal breeding and husbandry according to section 11 of the German animal protection law (Harlan-Winkelmann, Borcheln, Germany). All dogs were dewormed and vaccinated against rabies, distemper, parvovirus, leptospirosis, hepatitis and the parainfluenza virus. They were housed in an accredited facility in standard indoor and outdoor runs and were provided commercial dog chow and tap water *ad libitum*. dog leukocyte antigen (DLA)-identical donor/recipient pairs were selected on the basis of matching for highly polymorphic MHC class I and II microsatellite markers as well as for single-strand conformation polymorphism for the DLA-DRB1 allele.^{4,11}

Hematopoietic stem cell transplantation

Dogs received a single dose of 1 Gy ($n = 7$) or 2 Gy ($n = 5$) TBI at a dose rate of 0.25 Gy/min from a high-energy linear accelerator for conditioning within different transplant protocols.¹² Bone marrow of DLA-identical littermates was collected from the humerus and femur under general anesthesia and infused intravenously within 24 h after TBI. All dogs were given postgrafting immunosuppression consisting of CsA (Sandimmun Optoral; Novartis, Nürnberg, Germany) at 15 mg/kg orally two times daily on days -1 to 35 in combination with MMF (CellCept; Roche) at three different doses: 10, 20 and 30 mg/kg MMF orally two times daily on days 0–27 after transplantation. The clinical status of recipients was assessed twice daily.

Pharmacokinetic analysis

After being fasted overnight dogs received MMF and CsA, both as an oral solution. Food was withheld for an additional 2 h. Whole blood samples for pharmacokinetic analyses were collected from 10 dogs on day 14 (10, 20 mg/kg MMF) and day 27 (30 mg/kg MMF), respectively, in EDTA tubes before and 0.3, 0.7, 1.25, 2, 3, 4 and 12 h after drug administration for each MMF dose. In addition, 20 mg/kg MMF kinetic profiles were assessed on days 2 and 27 after transplantation ($n = 4$, each). All samples were stored immediately at 4 °C for a maximum of 24 h prior to

analyses. Total MPA plasma levels were quantified by enzyme multiplied immunoassay technique (EMIT assay, Dade Behring, Marburg, Germany). Pharmacokinetic parameters of MPA were calculated by noncompartmental analysis using Kinetica 4.2 (Inna Phase, Philadelphia, PA, USA). MPA AUC from 0 to 12 h (AUC_{0-12h}) was determined by use of the linear trapezoidal rule. The terminal rate constant (k_{el}) was estimated by log-linear regression using at least the last three data points. Elimination half-life ($t_{1/2}$) was thereafter calculated using $t_{1/2} = 0.693/k_{el}$. The apparent oral clearance (Cl/F) was determined by using the equation $Cl/F = \text{dose}/AUC_{tot}$. The apparent volume of distribution during the terminal phase (V_z) was estimated by using: $V_z = \text{dose}/(AUC_{tot} \times k_{el})$. The minimum and maximum plasma concentrations (C_{0h} and C_{max}) and the time to reach C_{max} (t_{max}) were directly derived from the data. In addition, whole blood concentrations of CsA were analyzed in parallel with the MMF pharmacokinetics 0 and 2 h after dosing at days 2, 14 and 27 by a fluorescence-polarization immunoassay.

Toxicity

Toxicity was evaluated from day 0 to day 35 (time of drug administration) after HSCT by assessment of activity, diarrhea, ingestion and weight loss. Grade of activity and ingestion was determined according to the following score: grade 0 = normal, grade 1 = reduced, grade 2 = no activity or ingestion, respectively. Diarrhea was graded as follows: grade 0 = normal stool, grade 1 = loose stool, grade 2 = diarrhea, grade 3 = bloody stool. The grading of weight loss was established according to the following criteria: grade 0 \leq 0.1% loss of body weight per day, grade 1 = 0.1–0.5% weight loss per day, grade 2 \geq 0.5% weight loss per day always in regards to starting weight.

Statistical analysis

The distribution of pharmacokinetic measures was described using medians and ranges. Comparisons of pharmacokinetic parameters between treatment groups were performed by using the Mann–Whitney *U*-Test. Within the treatment groups pharmacokinetic profiles of different days were analyzed by the Wilcoxon matched-pairs signed rank test. Correlations between pharmacokinetic parameters were evaluated using the Spearman's rank correlation coefficient. Data were considered to be statistically significant at $P < 0.05$.

Results

MMF pharmacokinetics at different dose levels and time points after HSCT

The pharmacokinetic parameters of total MPA after administration of different doses of MMF are presented in Figure 1 and Table 1. Following oral administration the plasma concentration-time profile showed an early peak at a median 0.7 h. The characteristic secondary peak normally induced by enterohepatic recirculation 6 to 12 h after MMF administration in SOT was not observed in two dogs of the 10 mg/kg group, from whom blood samples were

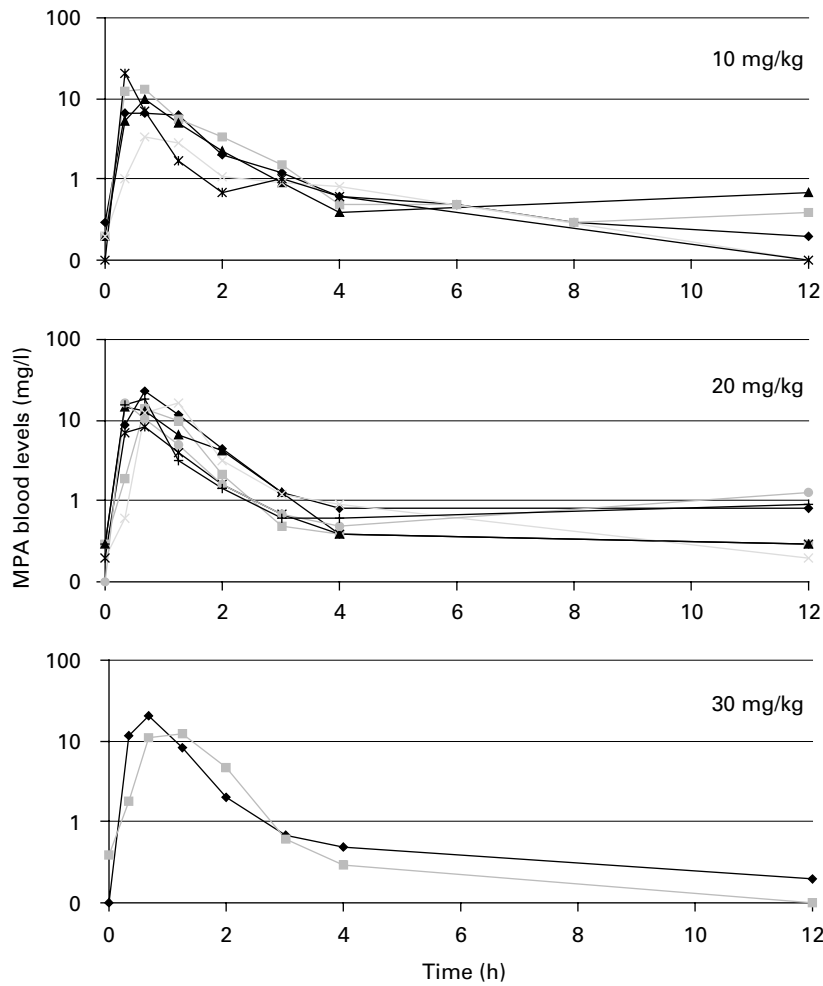


Figure 1 Individual MPA plasma concentration-time profiles after oral application of MMF in dogs receiving 10, 20 and 30 mg/kg MMF, respectively, and 15 mg/kg CsA twice daily after HSCT ($n = 5, 7$ and 2 , respectively). MPA = mycophenolic acid; MMF = mycophenolate mofetil.

Table 1 Pharmacokinetic parameters of total MPA in dogs receiving 10, 20 and 30 mg/kg mmF, respectively, and 15 mg/kg CSA twice daily after hematopoietic stem cell transplantation

	C_{0h} (mg/l)	C_{max} (mg/l)	t_{max} (h)	AUC_{0-12h} (mg/lh)	Cl/F (l/h/kg)	V_z (l/kg)	half-life (h)
10 mg/kg MMF (n = 5)							
Median	0.2	10.0	0.7	15.5	0.61	2.6	2.9
Range	0.1–0.3	3.4–20.2	0.3–0.7	9.7–21.6	0.43–0.99	0.9–4.1	0.8–4.8
20 mg/kg MMF (n = 7)							
Median	0.2	16.0	0.7	18.4	0.86	2.7	2.9
Range	0.0–0.3	8.5–22.5	0.3–1.3	13.9–33.1	0.57–1.32	1.1–16.8	0.7–14.2
30 mg/kg MMF (n = 2)							
Median	0.3	16.7	0.9	22.5	1.28	8.5	4.6
Range	0.1–0.4	12.3–21.0	0.6–1.3	20.8–24.3	1.16–1.41	8.0–9.0	4.0–5.3

Abbreviations: AUC_{0-12h} = area under the curve from 0 to 12h; C_{0h} = blood trough level; Cl/F = apparent oral clearance; C_{max} = maximal plasma concentration; half-life = elimination half-life; MMF = mycophenolate mofetil; t_{max} = time to reach C_{max} ; V_z = apparent volume of distribution during the terminal phase.

additionally collected at 6 and 8 h after dosing. Hence, both time points were canceled in further sampling. Using an adjusted body weight dosage, interindividual variations of MPA AUC_{0-12h} of maximum threefold were recorded. There were no significant differences between treatment

groups in any investigated pharmacokinetic parameter. However, dose escalation tended to increase plasma AUC from 15.5 to 22.5 mg/lh, concentration at steady state (C_{ss}) from 1.3 to 1.9 mg/l and V_z from 2.6 to 8.5 l/kg ($P = 0.190, 0.190, 0.095$, respectively), although a concurrent tendency

for a rise in plasma MPA clearance from 0.61 to 1.28 l/h/kg was observed ($P=0.095$). The doses applied had no linear association with plasma MPA concentration or blood trough level. Also MPA blood trough level did not correlate to AUC. Correlation analyses revealed highly significant associations between AUC and MPA concentration at 0.7, 1, 2, 3 and 4 h, respectively (Table 2).

At a dose of 20 mg/kg MMF the pharmacokinetic measurements were performed at different days after HSCT in order to determine differences over time. Significant differences over time were not detected for any of the pharmacokinetic parameters as shown in Table 3 and Figure 2.

Evaluation of toxicity was done for the parameters activity, diarrhea, ingestion and weight loss (Figure 3). In every dog gastrointestinal toxicities were temporarily observed that were characterized mainly by loose stools (grade 1) and only exceptionally by diarrhea (grade 2). Comparison between treatment groups showed no significant changes in diarrhea frequency. However, in two additional dogs that received MMF prior to this study dose elevation from 10 to 30 mg/kg caused increased diarrhea frequency that made a dose reduction necessary. Doubling the dose from 10 to 20 mg/kg MMF caused no changes in activity and ingestion. Whereas dogs of the 10 mg/kg group had stable weights, dogs of the 20 and 30 mg/kg group experienced weight losses during MMF treatment (0.2% per day ($P=0.003$) and 0.6% per day ($P=NS$), respectively). Total median weight of the three groups were as follows: 10 mg/kg: day 0 = 11.2 kg; day 35 = 11.8 kg; 20 mg/kg: day 0 = 13.8 kg, day 35 = 13.2 kg; 30 mg/kg: day 0 = 13.9 kg, day 35 = 12.8 kg. Dogs at 30 mg/kg had a reduced (\geq grade 1) activity and ingestion while on treatment (32 and 49% of all treatment days, respectively). In summary, dose-limiting toxicities from MMF were noted at the dose of 30 mg/kg MMF twice daily.

Table 2 Correlation coefficients (r) between MPA AUC_{0-12h} and each MPA concentration

	0 h	0.3 h	0.7 h	1 h	2 h	3 h	4 h	12 h
r	0.304	0.204	0.644	0.685	0.664	0.611	0.598	0.457
P -value	0.131	0.317	0.000	0.000	0.000	0.001	0.001	0.019

Table 3 Pharmacokinetic parameters of total MPA after oral application of 20 mg/kg MMF in combination with 15 mg/kg CSA twice daily at different days after hematopoietic stem cell transplantation

	C_{0h} (mg/l)	C_{max} (mg/l)	t_{max} (h)	AUC_{0-12h} (mg/lh)	Cl/F (l/h/kg)	Vz (l/kg)	half-life (h)
Day 2 (n=4)							
Median	0.3	13.5	0.7	18.6	1.13	6.4	3.8
Range	0.2–0.5	9.3–24.8	0.3–1.3	11.5–26.1	0.78–1.68	2.8–9.6	2.7–4.0
Day 14 (n=4)							
Median	0.2	16.0	0.7	16.8	1.15	2.6	1.8
Range	0.1–0.3	8.5–18.4	0.3–1.3	13.9–25.5	0.75–1.32	1.1–5.5	0.7–3.6
Day 27 (n=4)							
Median	0.5	9.9	0.7	21.3	0.79	6.7	6.6
Range	0.3–1.9	8.6–15.0	0.7–1.3	20.3–29.8	0.41–0.91	5.9–8.4	4.9–10.0

Abbreviations: AUC_{0-12h} = area under the curve from 0 to 12 h; C_{0h} = blood trough level; Cl/F = apparent oral clearance; C_{max} = maximal plasma concentration; half-life = elimination half-life; t_{max} = time to reach C_{max} ; Vz = apparent volume of distribution during the terminal phase.

CsA pharmacokinetics at different MMF dose levels and at distinct time points after HSCT

Cyclosporin A whole blood concentrations were estimated using a constant CsA dose of 15 mg/kg in combination with different MMF doses. Comparing the three MMF treatment groups (10, 20 and 30 mg/kg) no significant differences in CsA concentrations were detected (data not shown). Data obtained at different times after HSCT in the 20 mg/kg MMF group showed a tendency for CsA accumulation at day 27 compared with day 2. There were no significant median increases in C_{0h} and C_{2h} from 478 ng/ml (range 286–580) to 1033 ng/ml (range 617–1411) and from 1949 ng/ml (1795–2181) to 3099 ng/ml (2700–3699), respectively (Figure 4; $P=0.068$, each).

Discussion

Mycophenolic acid pharmacokinetics have been extensively studied in SOT, particularly after kidney transplantation. The relationships between pharmacokinetic MPA parameters and clinical outcomes such as organ rejection, toxicities, and infections have been evaluated leading to establishment of a target AUC_{0-12h} range of 30–60 μ g/ml h and a target MPA blood trough level between 1 and 3.5 μ g/ml for renal transplantation as originally proposed by Shaw *et al.*¹³ Pharmacokinetic studies in HSCT by Giaccone *et al.*⁸ showed that total MPA C_{ss} less than 2.5 μ g/ml, which correspond to an AUC_{0-12h} of less than 30 μ g/ml h, correlated with graft rejection. Therefore, the recommended target AUC seems transferable into HSCT as well. After allogeneic HSCT, alterations in pharmacokinetics of MPA were reported, which was mainly reflected by shortened half-lives and the resulting lower AUC. In clinical HSCT studies plasma MPA half-lives ranging from 1 to 4 h were observed.^{5,14–16} In contrast, the average plasma half-life in liver and renal transplant patients is about 6 and 11 h, respectively.^{17,18} For healthy adults half-lives of about 16–18 h were determined.^{19,20} In consequence, similar MMF doses as used in SOT achieved lower AUC values in the range of 10–30 μ g/ml h and C_{min} levels < 1 μ g/ml.^{5–7,14–16}

In accordance with these clinical data we found in our study total MPA AUC_{0-12h} and median blood trough levels below the recommended target ranges and shortened

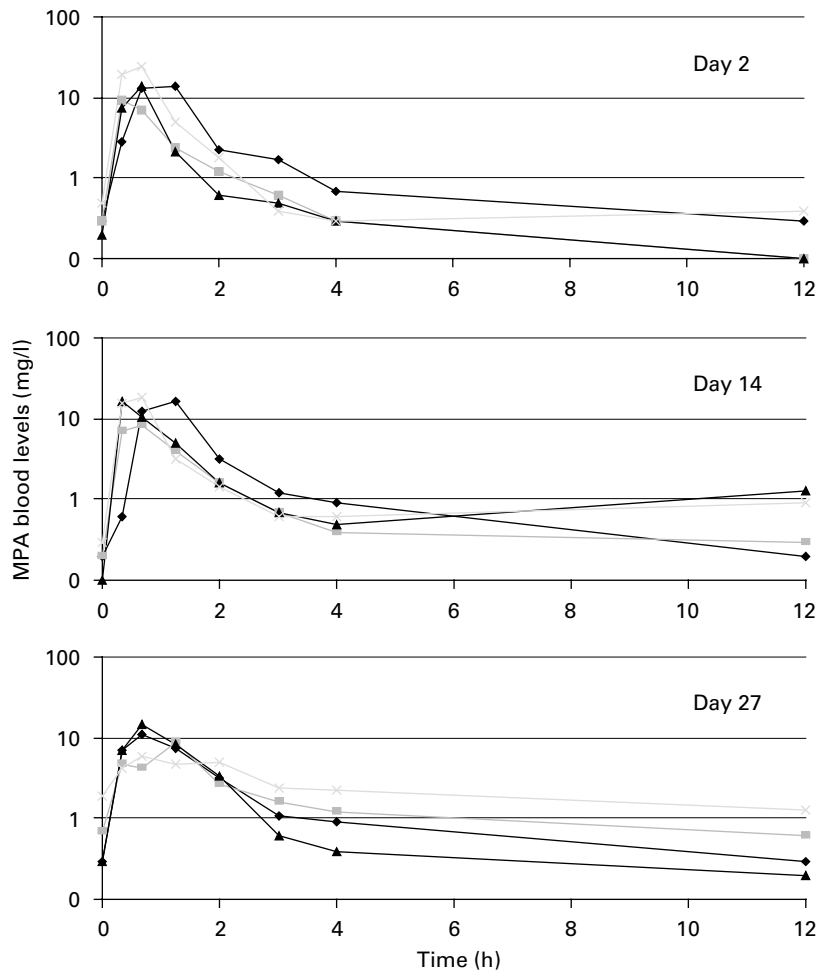


Figure 2 Individual MPA plasma concentration-time profiles after oral application of 20 mg/kg MMF in combination with 15 mg/kg CsA twice daily at different days after HSCT ($n=4$). MPA = mycophenolic acid; MMF = mycophenolate mofetil.

median half-life as well. Body weight-adjusted apparent oral clearance of MMF following HSCT seems to be comparable between dogs and humans.¹⁶ As in healthy humans a longer median MPA half-life and a considerably higher AUC of 8.1 h and of 62.3 mg/lh were calculated in healthy dogs,²¹ respectively, demonstrating the comparability of the canine HSCT model with the clinical situation.

Former studies in healthy dogs showed that the canine plasma concentration-time profile after oral MMF administration is characterized by a second peak between 4 and 12 h after dosing due to enterohepatic circulation.^{21,22} In the present study, only two dogs were analyzed after nonmyeloablative HSCT in this time frame and a secondary maximum could not be observed. In fact, MPA concentrations at 4 h were already in the range of lower limit of detection. The impairment of enterohepatic recirculation after myeloablative and nonmyeloablative HSCT was observed in clinical studies as well.^{6,7,14-16} On the one hand this may occur due to the gastrointestinal toxicity of the preceding conditioning regimen. On the other hand the CsA-MPA drug interaction may account for this phenomenon. CsA, the most widely used concomitant immunosuppressive agent in HSCT, was shown

to decrease MPA trough levels in kidney transplantation.²³ CsA inhibits biliary excretion of MPAG, which leads to a reduced reappearance of MPA in plasma. Therefore, minimal or no enterohepatic recirculation of MPA occurs.^{24,25} The absence of enterohepatic recirculation may reduce MPA AUC by up to 40%. However, in renal transplant patients that receive CsA in combination with MMF adequate plasma levels of MMF can be achieved in contrast to HSCT recipients.²⁶ Possibly this difference is due to higher CsA levels used in HSCT. Though, in a recent HSCT study no significant difference in MMF bioavailability could be observed between patients with CsA troughs ≥ 300 versus < 300 ng/ml.¹⁵ However, MPA levels in this study demonstrated up to eightfold interpatient variability underlying the diversity of MPA pharmacokinetics in the HSCT setting.

Reduction of MPA plasma levels could originate from a general poor absorption rate of MMF because of the gastrointestinal toxicity of the conditioning therapy. However, our data analyzing the AUC_{0-12h} at different days after HSCT do not support this hypothesis. In our study the highest calculated AUC_{0-12h} of 33.1 mg/lh occurred in the 20 mg/kg MMF group and was the only value that reached the lower limit of the recommended therapeutic

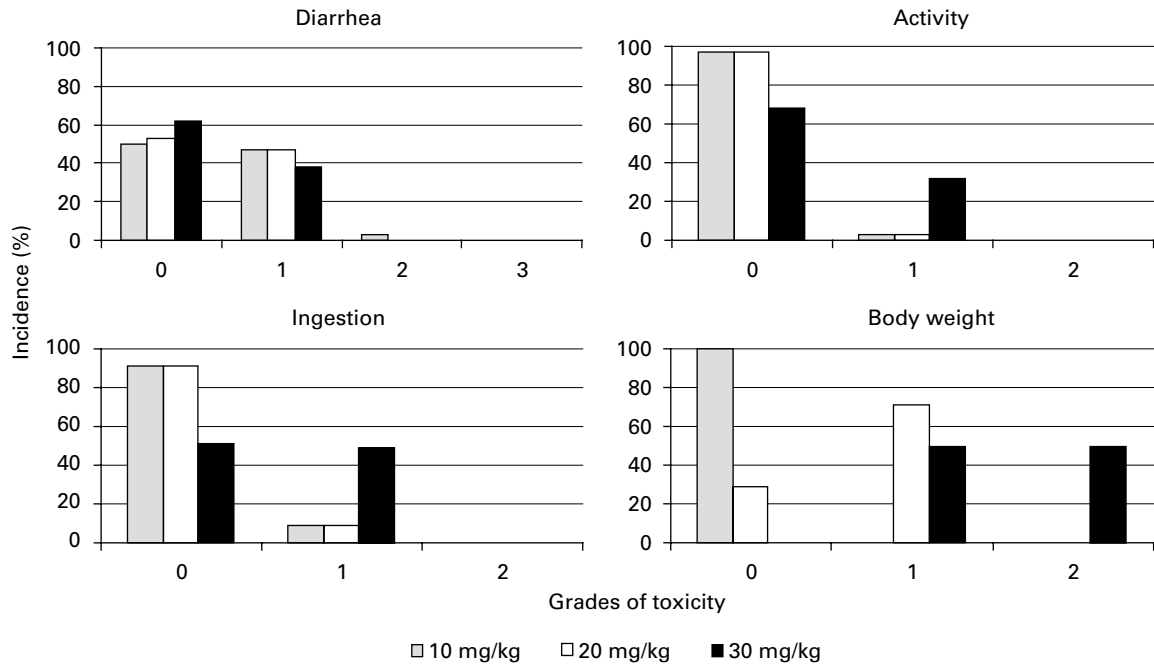


Figure 3 Toxicity of MMF in dogs after oral application of 10 mg/kg (gray), 20 mg/kg (white) and 30 mg/kg MMF (black), respectively, and 15 mg/kg CsA twice daily after HSCT ($n = 5, 7$ and 2 , respectively). Median occurrence of diarrhea, activity, ingestion and loss of body weight are pictured as toxicological parameters. Grading: diarrhea, 0 = normal stool, 1 = loose stool, 2 = diarrhea, 3 = bloody stool; activity and ingestion, 0 = normal, 1 = reduced, 2 = none; weight loss, 0 = $<0.1\%$ per day, 1 = $0.1-0.5\%$ per day, $2 \geq 0.5\%$ per day.

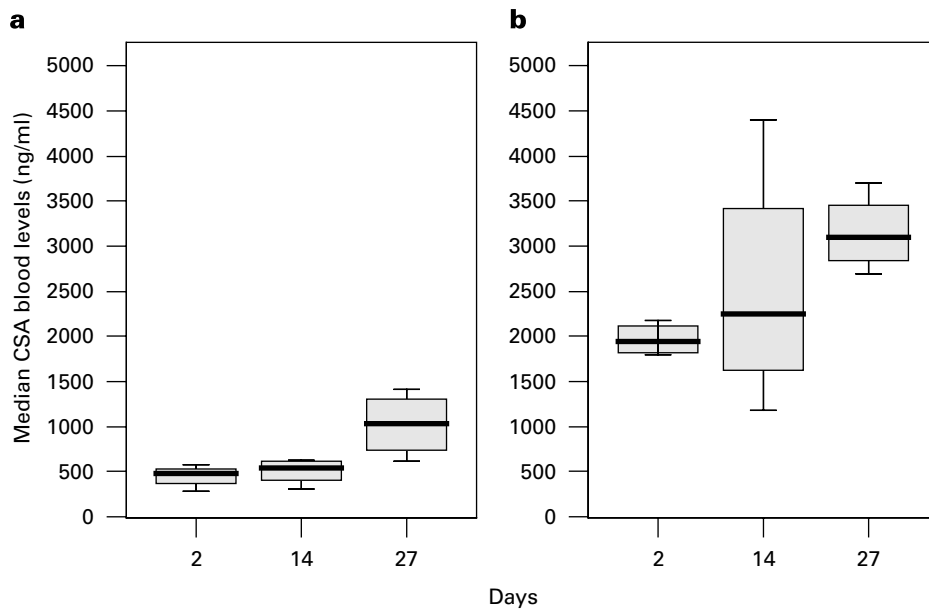


Figure 4 Median C_{0h} (a) and C_{2h} (b) values of CsA on days 2, 14 and 27 after HSCT following oral administration of 15 mg/kg CsA concomitantly with 20 mg/kg MMF twice daily ($n = 4$). Each data point represents median, lower and upper quartile, and the smallest and largest observation. CsA = Cyclosporine A.

range. No linear relationship between applied MMF dose and plasma MPA concentration was detected. Different absorption capacity due to gastrointestinal disorder may therefore be responsible. Moreover, calculated short half-lives impeded MPA accumulation over time. Similarly, studies in humans showed comparable MPA pharmacokinetics at different times after transplantation although

those studies used partially different time points for analyses compared to our study.^{5,8} Based on the short MPA half-life after HSCT more effective blood trough levels and AUC might only be reached by shortening the oral administration interval or parenteral drug application. MMF administration three times a day has indeed been found to optimize MPA exposure in patients undergoing

HSCT^{8,14,27} and correlated with a higher degree of donor T-cell chimerism and increased engraftment rate compared to patients receiving MMF twice daily.^{8,28}

Pharmacokinetic clinical trials in HSCT are limited and used mainly fixed doses of MMF in transplant patients. They observed large interindividual variabilities in MPA AUC ranging from 5- to 10-fold.^{6,29} Giaccone *et al.*⁸ found variabilities of MPA AUC in the range of seven- to eightfold despite using an adjusted ideal body weight dosage. Nevertheless, in our study a body weight adjusted dosing was performed as well, resulting in a 2.5-fold interindividual variability in the 20 mg/kg MMF treatment group and even smaller variabilities in the 10 and 30 mg/kg groups. Therefore we conclude that dosing by body weight might be favorable. Combining body weight-adjusted dosing with MMF administration at least three times daily adjustment of MPA blood trough level and AUC to the targeted window should be facilitated. In combination with routine drug monitoring, improvement of immunosuppression at tolerable side effects should be possible.

Measurement of MPA AUC using a full set of samples is very time consuming and requires considerable quantities of blood. Hence, the association between AUC and MPA level at single time points is of particular clinical interest. Present data revealed that MPA blood trough level did not accurately describe MPA AUC and, therefore, the clinical usefulness of the trough level appears to be limited. The significant correlations detected at later times are medium and therefore using a single concentration is critical for estimation of MPA AUC. The highest correlation coefficients were calculated at 0.7, 1 and 2 h. Samples at these time points may be applicable for development of an abbreviated sampling scheme for reliable estimation of MPA AUC in the HSCT dog model as well as in humans.

The influence of MMF on CsA pharmacokinetics is controversially discussed. In pediatric renal transplantation, patients treated with CsA and MMF had significantly lower C_{2h} levels and required higher CsA doses to reach similar AUC compared to patients treated with CsA only.^{30,31} In contrast, results by John *et al.*³² showed higher C_{2h} values with a lower CsA dose using immunosuppression with CsA and MMF. In our study, the pharmacokinetic parameters of CsA were investigated at various MMF doses. No significant differences between the three MMF treatment groups in C_{0h} and C_{2h} of CsA were observed. These data are substantiated by the findings of Pape *et al.*³¹ whose results showed no correlation between MMF AUC and CsA AUC. Therefore, a dose-dependent effect of MMF on CsA metabolism seems unlikely. Nevertheless, our data indicated that application of a constant CsA dose may cause a time-dependent increase in pharmacokinetic parameters of CsA. Whether this increase was caused by simultaneous administration of MMF or whether the relative high C_{0h} and C_{2h} values reached with a dose of 15 mg/kg twice daily by themselves caused an accumulation over time independently from MMF administration cannot be concluded from this study. Since the enhancement did not become visible until day 27 and the administration of CsA ends in this HSCT setting at day 35, no dose adjustment was performed.

In conclusion, the canine HSCT model clearly indicates fundamental similarities in the pharmacokinetic profile of MMF to humans. Particularly the pharmacokinetic variables AUC, blood trough level, half-life, apparent oral clearance, and enterohepatic recirculation provided very good comparability to the clinical setting underlying the suitability of this model. In detail, our study showed that achievement of the recommended therapeutic range for MMF was not feasible in a canine HSCT model with a twice daily regimen. Oral administration of 20 mg/kg MMF two times a day after nonmyeloablative allogeneic HSCT in dogs was safe but not sufficient to reach MPA AUC above 30 mg/lh. Higher MMF doses did not significantly enhance MPA blood level but were less well tolerated as they reduced activity, ingestion and body weight. Hence, for more effective MPA levels a shortening of the administration interval and/or a change in route of administration is necessary. A body weight-adjusted dosing may be helpful in minimizing interindividual variability but cannot substitute for routine drug monitoring, since in a body weight-adapted regimen intra- and interindividual variations also occurred. Further studies of MMF metabolism after HSCT are needed to optimize the dosing schedule in order to achieve a reliable immunosuppression and less toxic side effects.

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